Study protocol

Title of project: Using thermal clothing to reduce heart failure morbidity during winter

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AIM

To examine if wearing thermal clothing improves the health of heart failure patients during winter.

SIGNIFICANCE

Our recent study estimated that 6,500 years of life are lost each year in Brisbane due to temperature-related deaths [1]. Around 5,000 of these lost years are due to low temperatures (mean daily temperature below 23°C). A recent *Lancet* estimated that 6.5% of all deaths in Australia are due to exposure to low temperatures, with only 0.5% due to high temperatures [2]. As well as winter deaths, there are many extra hospitalisations during winter, and most Brisbane hospitals experience a "winter bed crisis". Despite the great health burden of cold weather, there has been only one previous intervention in Queensland targeted towards reducing the effects of cold temperatures, and this was our pilot study [3].

We believe that many cold-related deaths and hospitalisations could be avoided if people took simple preventative measures (this is particularly true for the elderly and those with pre-existing cardiovascular or respiratory disease, as these groups are the most susceptible to the weather). In this study we will investigate if a simple improvement in clothing can improve health during winter.

HYPOTHESES

Primary hypothesis

Heart failure patients who receive thermal clothing will spend less time in hospital during winter compared with patients who receive no extra clothing. Winter is defined as lasting from 1 May 2016 until 30 September 2016, or after 1 May for participants recruited later.

Secondary hypotheses

Compared with heart failure patients who receive no extra care, patients who receive thermal clothing will:

- Report better quality of life.
- Report better sleep.
- Have lower blood pressure and other cardiovascular risk factors.
- Have a reduced risk of death.

Background

The association between daily average temperature and death in three Australian cities is shown in Figure 1. All three cities have U-shaped associations, with deaths increasing on hot and cold days (mostly cardiovascular and respiratory deaths). All three cities have a narrow "comfort zone", which indicates the populations' vulnerability to all but a narrow range of temperatures.

The seasonal pattern in cardiovascular disease deaths in the Australian capital cities is shown in Figure 2 [4]. Cardiovascular deaths peak in July, and are lowest in February. Heart failure death rates are 23.5% higher in August compared with the annual average [4]. The seasonal increase in heart failure has the strongest seasonal pattern compared with six other categories of cardiovascular disease: hypertensive disease, ischemic heart disease, electrical conduction system, pulmonary and pulmonary circulation, cerebrovascular diseases and myocardium/cardiomyopathy.

The route from cold temperatures to heart failure deaths and hospitalisations is most likely via a rise in blood pressure. A clear link has been noted between low temperatures and increased systolic blood pressure [5, 6]. And the strength of this association has been shown to be greater in Australia and other warm climate countries [7]. The theory behind the paradoxically stronger link in warmer climates is that people in warmer climates do not adequately protect themselves against the cold compared with people in cold climates. This

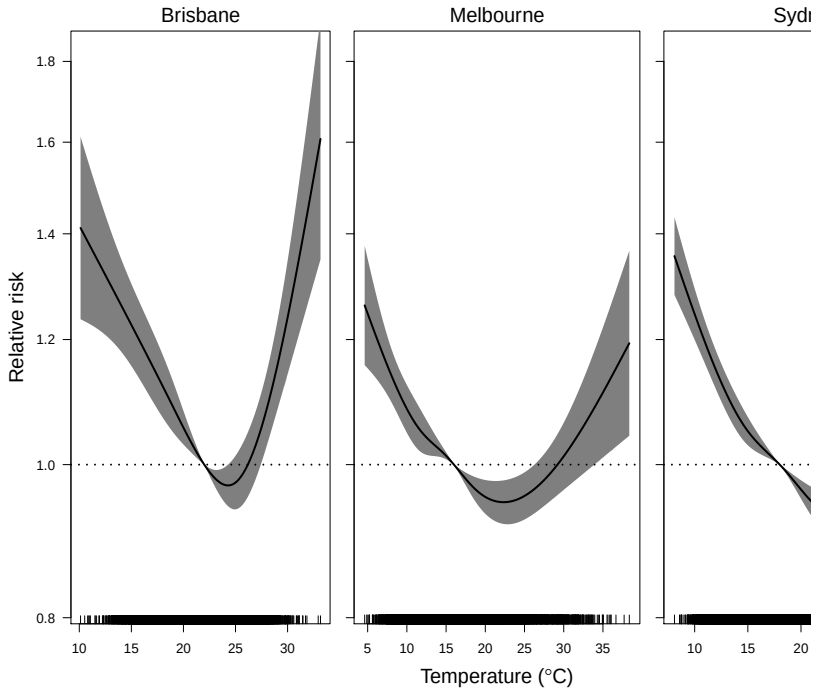

Figure 1: Associations between daily average temperatures and daily numbers of non-accidental deaths in Brisbane, Melbourne and Sydney, 1987–2009. The black lines are the means, and the grey areas the 95% confidence intervals

finding comes from the seminal Eurowinter study [8]. At a temperature of 7 °C, 72% of people in Southern Finland wore a hat, whilst only 13% of people in Athens did. People in warm European climates were also less likely to wear gloves and trousers in cold weather compared with people in cold climates. These findings from Europe are directly applicable to Australia, and our own research noted that the winter increase in cardiovascular deaths was smaller in Hobart than Sydney or Brisbane [4].

Home insulation has been shown to improve people's health during winter. A randomised controlled trial in New Zealand retrofitted houses with insulation in homes of people with respiratory disease [9]. The treatment group experienced significantly fewer hospitalisations, GP visits, days off school and days off work. A randomised controlled trial in Scotland upgraded flats that were cold, damp and mouldy to being comfortably warm [10]. The treatment group experienced statistically and clinically significant improvements in blood pressure and general health, and fewer hospital admissions. Our study aims to insulate the person rather than the whole house, but we anticipate similar improvements in health.

Wearing better clothing is a sustainable solution as it is relatively cheap and means that people can reduce their heating usage. Many heaters also create indoor air pollution (particularly wood or gas burners) which increases the risk of cardiovascular events [11]. Heaters in Australia often only heat one room, which means the benefit is lost when the person moves elsewhere. Wearing better clothing insulates the person regardless of their location.

Our instruction sheet for participants in the treatment group recommends wearing the

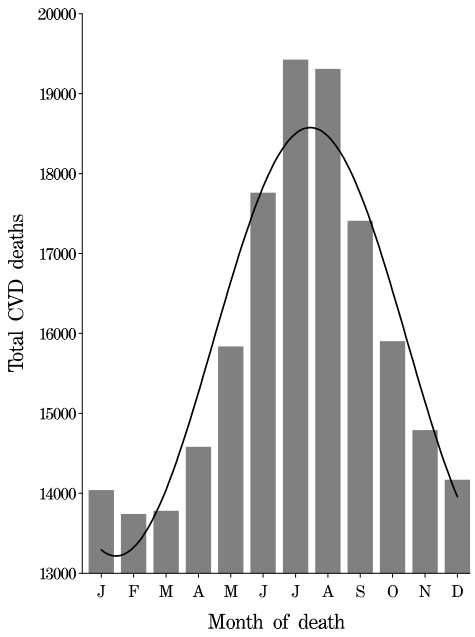

Figure 2: Total cardiovascular disease deaths in Australian capital cities (1997-2003) and fitted seasonal sinusoid.

thermals when the temperature is below 18 degrees Celsius. This threshold is based on our paper showing an increase in the risk of death in men and women below this temperature [1].

Outcome Measures

Primary outcome:

- Number of days in hospital during winter

Secondary outcomes:

- Overall health service usage during winter
- Number of GP visits during winter
- Quality of life using the EQ-5D in midwinter and at the end of winter
- Sleep quality using the Pittsburgh sleep questionnaire in midwinter and at the end of winter
- Systolic blood pressure
- Four cardiovascular risk factors:
  - Blood viscosity
  - Cholesterol
  - Fibrinogen

  - c-reactive protein

- Death measured over 5 years of follow-up

All results will be for winter 2016. Midwinter will be in July, and the end of winter will be September.

Methods

Consent

Patients will be identified and approached in Dr Platts' cardiology clinic and cardiology wards at The Prince Charles Hospital. The approach and consent will be made by a research nurse.

Inclusion criteria

Patients will be eligible for inclusion if they:

- Have an ejection fraction below 45%
- Are older than 50 years

Exclusion Criteria

Patients will be excluded if they:

- Are pregnant (highly unlikely).
- A serious co-morbidity (e.g., cancer) or a serious physical impairment that prevents the participant from dressing themselves.
- Live in a residential care facility.
- Are unable to give informed consent.
- Were involved in our previous pilot.

Randomisation

We aim to recruit 120 patients who will be randomised to receive the thermals or not. A randomisation list will be created using the R software (`www.r-project.org`). The list will be in randomly permuted blocks of 2, 4, 6 and 8 in a 1:1 ratio using the 'blockrand' function [12]. We will stratify by recruitment location (ward/clinic) because of the higher risk of subsequent events for ward patients.

The randomised list will be loaded into the REDCap (Research Electronic Data Capture) data management software [13]. The nurse will first complete the informed consent procedure and baseline questionnaire using a computer tablet. The random allocation will then automatically occur once they reach the end of the baseline questions. The

randomisation list will be created by the study statistician, and only they will be able to view the randomised groups.

If the participant is randomised to the treatment group the nurse will then give the patient:

1. Two thermal tops, one thermal hat and two pairs of thermal socks.
2. A large display digital thermometer with batteries fitted.
3. An advisory sheet on when to wear the thermals.

Patients in both groups will receive:

1. Two data loggers to automatically record indoor temperatures in participants' bedrooms and living rooms.
2. A clothing diary to prospectively record their clothing for one week in midwinter

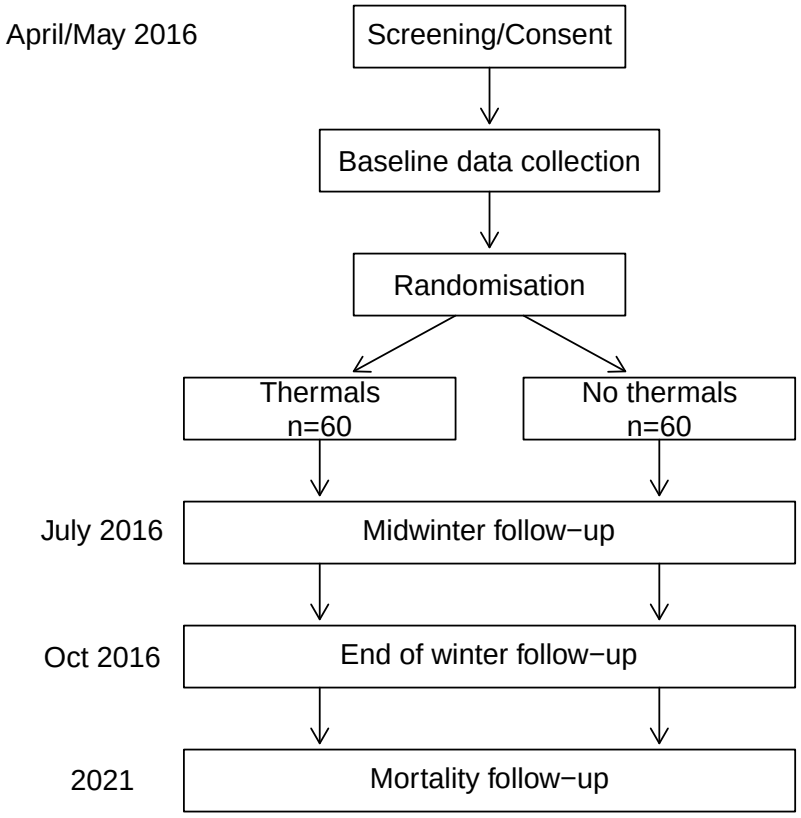

Figure 3: Diagram of participant flow

Data collection

We will use nine data sources linked using a unique study number:

1. Hospitalisations from Queensland public hospitals.
2. Emergency department contacts from Queensland public hospitals.
3. Data from the Medicare Benefits Schedule to get GP visits and hospitalisations from private hospitals
4. Blood tests to collect cardiovascular risk factors at baseline and follow-up
5. A baseline interview to collect demographic data and baseline quality of life and sleep
6. Telephone follow-ups to collect data on quality of life, sleep and the participants' homes (by research staff who are blind to the intervention group)
7. Clothing diaries to get follow-up data on daily clothing during one week in midwinter
8. Temperatures inside participants' homes using Thermocron® data loggers
9. Death date from the National Death Index

Data sets 1 and 3 will be combined to give the primary outcome of hospitalisation stay during winter. Data sets 1 to 3 will be combined to give the secondary outcome of overall health service usage during winter.
The data collection times are shown in Figure 4.

Statistical Analysis

Data will be analysed using an intention-to-treat approach, so if a participant in the thermal group did not wear the thermals, they will be still be included in the final analysis as a member of the thermal group. We will also run a per protocol analysis, where these patients are excluded to give an idealised estimate of the treatment effect. The compliance data will come from the clothing diary. Participants in the thermal clothing arm will be excluded from the per protocol analysis if they:

- Fail to return the diary
- *Or* return the diary and report no use of the thermals.

All outputs (tables and graphs) will be initially created using a scrambled treatment group as an attempt to find coding errors or statistical issues. The results will then be presented to the investigator using a blinded treatment group ('A' and 'B') in order to get an unbiased interpretation of any difference between the groups.

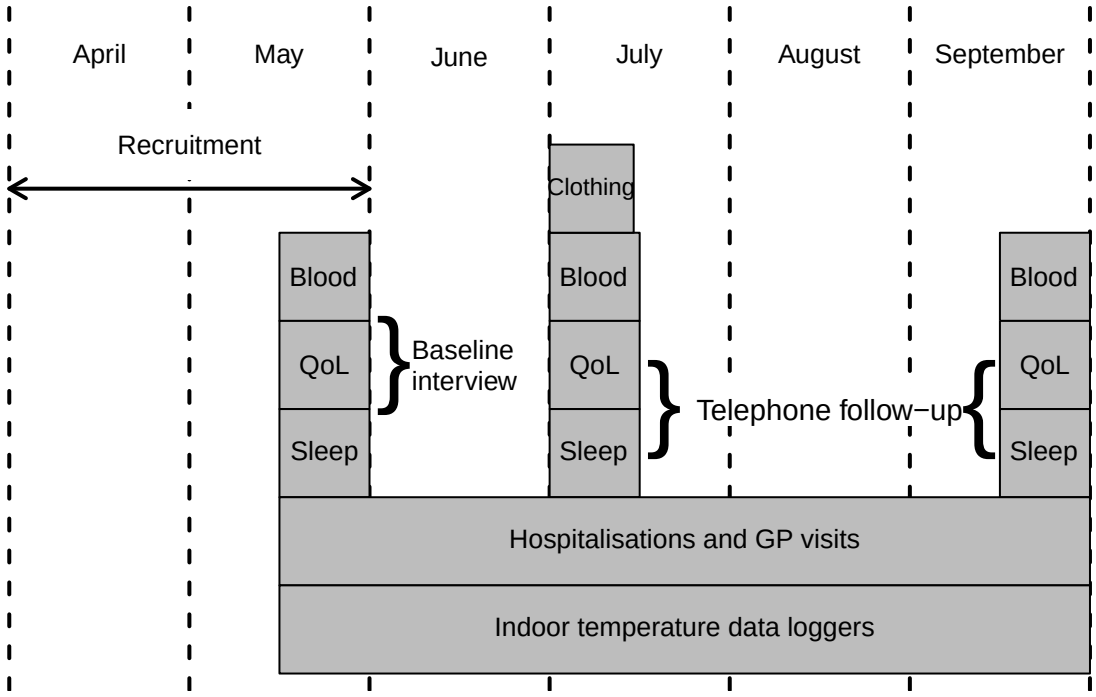

Figure 4: Summary of the data collection over time, showing example times for a participant recruited in mid-May with telephone follow-ups in July and September. Based on Bureau of Meteorology data for the last 10 years, the coldest day (on average) was 30 June in Brisbane.

Primary outcome

We will compare the number of days in hospital between the two groups using the bias corrected bootstrap to create non-parametric 95% confidence intervals for the difference between the mean number of days in hospital between the two groups [14]. A parametric analysis would be a Poisson regression model with a dependent variable of number of days and independent variable of treatment group. However, in the pilot study we could not use the Poisson model because the assumption of independence between days was violated [3].

We will include no other independent variables because we do not expect any confounding given that the treatment is randomised. To control for the differing lengths of observation times between patients we will divide each participant's total number of days in hospital by their number of days under study [15]. This is important because some participants may not be recruited until June.

Secondary outcomes

We will compare the number of GP visits during winter using the same method as per the primary outcome. We will compare quality of life in midwinter and the end of winter using a mixed model with the quality of life score as the dependent variable, treatment group as the key independent variable, baseline quality of life as an independent variable and a random intercept to control for the within-participant correlation. This same analysis of covariance (ANCOVA) model will be used to compare sleep quality, blood pressure and the

cardiovascular risk factors.

We will compare the indoor temperatures using a multivariate model with living room and bedroom temperatures as the dependent variable and independent variables for treatment group, time of day and time during winter. The model will include a random intercept to control for the repeated data from each participant.

For each participant we will convert their clothes worn during the day and night into a 'clo' score [16]. We will compare the scores between treatment groups using a mixed model with a random intercept for each participant. We will run separate models for day and night time wear.

We will examine whether thermal clothing reduced the risk of death by sending our participants details to the National Death Index in 2021, five years after the end of the active monitoring phase. We will use a survival analysis with a Kaplan–Meier plot and log-rank test to compare the survival of the two groups.

We will use a Bayesian perspective and hence give the probability that the treatment group is superior to the control group. All analysis will be conducted using the latest version of R `www.r-project.org` together with WinBUGS for the Bayesian analyses [17].

Planned interactions

The consent process itself may impact on the efficacy of a behavioural intervention, known as a "research participation effect" [18]. To test this we will ask the research nurse to gauge the enthusiasm of the participant at baseline using a three-level scale. We will then examine an interaction between the intervention and this enthusiasm variable.

We will also examine an interaction between the date the participant enrolled and the intervention effect. This is because participants recruited early may have lost their thermals or forgotten about the trial by the time winter started.

We will also examine the influence of contact with the participants by examining if the indoor temperature readings changed after the midwinter phone call.

Power

Sixty participants per group gives us an 85% power to detect a halving in the average length of hospital stay during winter from 6 days in the control group to 3 days in the treatment group. We assumed a halving in hospital stays based on the halving in hospital admissions from a randomised controlled trial of home insulation [9].

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